Acute Renal Failure Due to Acute Tubular Necrosis Caused by Direct Invasion of Orientia tsutsugamushi

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We describe a scrub typhus patient with acute renal failure for whom a diagnosis was made based on serology as well as immunohistochemical (IHC) staining and an electron microscopic examination (EM) of a renal biopsy specimen. For our case, we demonstrated by IHC staining and EM that renal failure was caused by acute tubular necrosis due to a direct invasion of Orientia tsutsugamushi.

CASE REPORT

A healthy-looking, 33-year-old male patient received a drug treatment for a 2-week history of cough and sputum. One day before admission to our hospital, he complained of abdominal pain and nausea after he played football. He was suspected of having renal failure on examination at a local clinic and was transferred to Chosun University Hospital in Gwang-ju, South Korea. At the time of admission, his vital signs were a blood pressure of 120 over 80 mm Hg, a pulse rate of 72 times/min, a respiratory rate of 20 breaths/min, and a body temperature of 37.2°C. A urinalysis showed no gross hematuria, with a urine output of 50 ml/h. His mental status was alert. There was no skin rash or lymphadenopathy. The patient’s complete blood count showed a white blood cell count of 11,630/mm3, a hemoglobin count of 14.5 g/dl, and a platelet count of 243,000/µl. An arterial blood gas analysis showed a pH of 7.404, a partial CO2 pressure of 38.1 mm Hg, a partial O2 pressure of 79.4 mm Hg, an HCO3− concentration of 23.3 mmol/liter, and an O2 saturation of 95.8%. His serum biochemistry results were as follows: [Na+] 135 meq/liter; [K+] 4.2 meq/liter; [Cl−] 120 meq/liter; blood urea nitrogen, 39.3 mg/dl; and creatinine, 5.0 mg/dl. The biochemistry results showed a total protein level of 6.73 g/dl, albumin at 3.78 g/dl, aspartate transaminase at 30 IU/liter, alanine aminotransferase at 18 IU/liter, creatine phosphokinase at 446 U/liter, lactate dehydrogenase at 565 U/liter, myoglobin at 168.4 ng/ml, fibrin degradation products at 1 mg/ml (range, 0 to 5.0 mg/ml), and a D-dimer concentration of 143.6 ng/ml (range, 0 to 255 ng/ml).

On urinalysis, hematuria (score, 1:4,096. A follow-up antibody test was performed to examine for the presence of concurrent diseases. The tests were all negative for rheumatoid factor, antinuclear antibody, antineutrophil cytoplasmic antibody, and cold agglutinin, human immunodeficiency virus, hepatitis B virus, and hepatitis C virus antibodies, and the VDRL test was negative. Antistreptolysin O and complement levels were all normal.

A self-employed person, our patient presented with no typical symptoms of scrub typhus, including rash, fever, and headache. He had a history of outdoor activity 10 days before admission. He had previously maintained a healthy life but had a markedly increased level of creatinine. He therefore received a renal biopsy for further evaluation and to make a differential diagnosis from other diseases, including rapidly progressing glomerulonephritis.

Tissue from the biopsy underwent immunohistochemical (IHC) staining and immunofluorescent staining, in which the primary antibody was ICR mouse hyperimmune serum immunized with Orientia tsutsugamushi strain Boryong at a dilution of 1:200. The antibody could detect other disparate strains of O. tsutsugamushi in addition to strain Boryong in the immunofluorescence assay (IFA) (data not shown). IHC staining was performed using a streptavidin-biotin immunoperoxidase method according to the supplier’s protocol (LSAB kit; Dako, Carpinteria, CA), as described previously (2). Using renal biopsy, IHC staining, immunofluorescent staining, and electron microscopic examination (EM), we identified the presence of Orientia tsutsugamushi coccobacilli within the tubule. Based on these findings, a diagnosis of scrub typhus was established for our patient. He was immediately given doxycycline. An IFA serological test was performed using paired sera (2). At the time of admission, the patient’s IFA serologic profile showed an immunoglobulin M (IgM) titer of 1:10 and an IgG titer of 1:4,096. One week after he was given doxycycline, samples from the recovery phase showed an IgM titer of 1:1,280 and an IgG titer of 1:4,096. A follow-up antibody test was performed to examine for the presence of concurrent diseases. The tests were all negative for endemic typhus, hemorrhagic fever with renal syndrome, leptospirosis, and measles. He recovered without any notable complications following doxycycline treatment. He was discharged when his serum creatinine levels returned to normal.
Patients with scrub typhus present with an eschar at the site of the mite bite, a maculopapular rash, fever, myalgia, headache, and anorexia (4). The prognosis varies between patients, ranging from asymptomatic infection to death. Because scrub typhus causes systemic vasculitis, it can cause meningitis, interstitial pneumonia, acute pulmonary edema, hepatitis, and acute renal failure in untreated cases (6, 7, 8, 9). Hematuria and proteinuria may occur because of renal invasion in 10 to 20% of patients with scrub typhus. Acute renal failure is not a common entity, but it is known to be one of the serious complications seen in patients with scrub typhus, spotted fever, or murine typhus (3, 5, 10). Fever, headache, and rash are potential indicators for rickettsial disease and are known to be useful clues for the diagnosis of scrub typhus (1). However, our patient visited us with the chief complaint of a prompt deterioration of renal function without the triad of symptoms of scrub typhus, including typical skin lesions, fever, and headache. To identify the cause of the prompt deterioration of renal function, a renal biopsy with IHC staining, immunofluorescent staining, and EM were performed. This established a diagnosis of scrub typhus. An early recovery was achieved following doxycycline treatment.

In our case, a renal biopsy showed that the capillary loop and cellularity were normal in the glomerulus. The renal tubules underwent multifocal tubular necroses, and foci of some mononuclear cells were identified in the infiltration of the tubulointerstitium. Tubular epithelial cells underwent degenerative changes and were detached from the basement membrane (Fig. 1). Epithelial casts were observed in some renal tubules. These histopathologic findings were suggestive of acute tubular necrosis with chronic tubulointerstitial nephritis.

Several hypotheses have been proposed to explain the mechanism by which O. tsutsugamushi infection causes acute renal failure. First, it is assumed that the pathophysiology of acute renal failure is associated with prerenal azotemia due to renal hypoperfusion in cases of shock or volume depletion. According to Dumler et al., prerenal azotemia is the main pathophysiology of renal failure caused by the decrease of effective renal blood flow due to increased vascular permeability in patients with murine typhus accompanied by systemic vasculitis (1). Hypoalbuminemia is commonly noted to occur in patients with rickettsial disease. This has been reported to be due to the leakage of plasma albumin into the perivascular space because of widespread vascular damage (1). In our case, however, there was no clear evidence of decreased blood pressure or other signs and symptoms suggestive of volume depletion, including diarrhea and vomiting. Furthermore, our patient had a normal range of serum albumin levels. This led to the speculation that acute renal failure did not occur due to prerenal azotemia in our patient. Second, disseminated intravascular coagulation (DIC) is considered another pathophysiologic trait of renal failure. To put this another way, renal failure is caused by the decrease of effective renal blood flow due to increased vascular permeability in patients with murine typhus accompanied by systemic vasculitis (1). Hypoalbuminemia is commonly noted to occur in patients with rickettsial disease. This has been reported to be due to the leakage of plasma albumin into the perivascular space because of widespread vascular damage (1). In our case, however, there was no clear evidence of decreased blood pressure or other signs and symptoms suggestive of volume depletion, including diarrhea and vomiting. Furthermore, our patient had a normal range of serum albumin levels. This led to the speculation that acute renal failure did not occur due to prerenal azotemia in our patient.
Walker and Mattern (7) and others (10) reported that histopathological findings were suggestive of multiple interstitial nephritis in patients with renal failure accompanied by murine typhus. Our patient also had acute tubular necrosis, in which numerous *O. tsutsugamushi* coccobacilli were deposited within his renal tubules, as determined by IHC staining, immunofluorescent staining, and EM. Furthermore, his renal function promptly recovered following doxycycline treatment. These findings support the possibility that the direct invasion of *O. tsutsugamushi* into renal tubules caused acute tubular necrosis and then resulted in acute renal failure. Neither acute glomerulonephritis, nontraumatic rhabdomyolysis with myoglobinuria, or DIC have so far been documented to contribute to the development of acute renal failure. Little is known about whether the development of renal failure is associated with DIC or acute glomerulonephritis. Further clinical studies are therefore warranted to examine the pathophysiology of acute renal failure in patients with scrub typhus.

In conclusion, our case highlights the following two points. First, in order to identify the cause of the prompt deterioration of renal function, a renal biopsy with IHC staining and EM was performed. The adequate use of IHC staining or EM established an early diagnosis of scrub typhus prior to serologic follow-up. Second, for our case, we demonstrated by IHC staining and EM for the first time that renal failure in patients with scrub typhus is caused by acute tubular necrosis due to the direct invasion of *O. tsutsugamushi*.

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We declare no commercial interest and do not belong to any association that might pose a conflict of interest for this work.

**REFERENCES**